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(54) Title: STABILIZED PHARMACEUTICAL COMPOSITION CONTAINING RABEPRAZOLE SODIUM WITH IMPROVED BIOAVAILABILITY

(57) Abstract: The present invention relates to stable pharmaceutical composition of rabeprazole sodium in a form of enteric coated pellets, either alone or in combination with one or more prokinetic agent, preferably mosapride in a form of sustained release tablets, in a single unit dosage form, which provides enhanced bioavailability of rabeprazole. Present invention also discloses process for preparation of said pharmaceutical formulation.

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STABILIZED PHARMACEUTICAL COMPOSITION CONTAINING RABEPRAZOLE SODIUM WITH IMPROVED BIOAVAILABILITY

FIELD OF THE INVENTION

The present invention relates to stable pharmaceutical composition comprising rabeprazole in a form of pellets either alone or in combination with one or more prokinetic agent in a sustained released form, wherein the said formulation provides enhanced bioavailability of rabeprazole in comparison to tablet formulation of rabeprazole.

The instant invention also relates to use of the said composition in the prevention and treatment of acid related gastrointestinal disorders, particularly disorders associated with gastroesophageal reflux.

Furthermore, the present invention refers to a method for the manufacture of said pharmaceutical composition.

BACKGROUND OF THE INVENTION

Gastro esophageal reflux disease (GERD) is among the most common disorders seen by gastroenterologists and general practitioners. Therapeutic agents effective in the treatment of GERD include gastric acid suppressing agents, such as H₂ receptor antagonists, proton pump inhibitors, other agents of interest are antacids/alginates and prokinetic agents. These agents can be distinguished by their mechanisms of action, safety profile, pharmacokinetics and indications.

Antacids and alginates are widely used option. They have a shorter duration of action and are seen as an inexpensive and safe option. However, they do not provide a long-term symptom resolution of GERD.

H₂ receptor antagonists are widely prescribed for GERD. They are

advantageous and offer more potent and a longer duration of action on gastric acidity.

Proton pump inhibitors, such as rabeprazole, are rapidly replacing H₂ receptor antagonists, for the treatment of GERD. Proton pump inhibitors are known to offer significant advantages over H₂ receptor antagonists in terms of symptom resolution, healing and prevention of relapse for GERD.

Rabeprazole is a substituted benzimidazole derivative, chemically known as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1*H*-benzimidazole as disclosed in US5045552 and EP268956B1. Rabeprazole belongs to a class of proton-pump inhibitors, that inhibits gastric acid secretion by inhibiting the enzyme H⁺, K⁺ ATPase at the secretory surface of the gastric parietal cell and is useful for the prevention and treatment of ulcers, gastro esophageal reflux disease (GERD or heartburn) and other conditions involving excessive acid secretion. The stability of rabeprazole sodium is a function of pH; it is rapidly degraded in acid media and is more stable under alkaline conditions.

Rabeprazole is unstable and prone to rapid decomposition and discoloration in the presence of moisture at neutral to acidic conditions. Various approaches in the art have been disclosed to prepare a stabilized formulation of rabeprazole.

WO2004014345 describes the pharmaceutical preparations of pellets containing a benzimidazole compounds with an inert core to which a layer containing an active ingredient is applied. To the said layer of active ingredient further layer is applied, preferably one or more inert layers (separating layers), which is optional. Further, the pellet has an outer layer comprising an enteric coat, that is, an enteric layer. The described pharmaceutical preparation achieves excellent storage stability, which is achieved by combining the benzimidazole compound in mixture with microcrystalline cellulose in the form of a layer containing an active ingredient on an inert core (a neutral pellet).

WO9712580 and WO9712581 describe and oral dosage forms of substituted benzimidazoles obtained by compression of pellets containing benzimidazole, thereby producing micro-tablets that are subsequently coated and placed inside hard gelatine capsules.

EP993830, US5626875 discloses a stable oral pharmaceutical preparation of benzimidazole compound comprising a nucleus formed by an inert core, the acid labile benzimidazole, an inert water soluble polymer and pharmaceutical acceptable excipients with the exclusion of alkaline reacting excipients; an inert coating disposed on said nucleus, formed by a water soluble polymer and other pharmaceutically acceptable excipients, with the exclusion of alkaline reacting excipients; and an outer layer on the previous coating comprising an enteric coating.

US6228400 discloses the pharmaceutical formulations containing an inert core, a drug emulsion layer of a free base of omeprazole or lansoprazole with a nonionic surfactant and water over inert core, a protective coating and an enteric coating

WO03077829 describes an oral pharmaceutical composition of an acid labile drugs characterized in a core containing acid labile drug, sub coat, a separating layer, seal coat is a layer which separate the sub coat with enteric coat and the enteric coating layer.

WO2002026210 and US 2003211147 describes a delayed-release, pharmaceutical capsule dosage form, which comprises one or several enteric-coated, compressed cores encapsulated by a capsule shell, wherein the enteric coated compressed core consists essentially of a mixture of a pharmaceutically acceptable carrier and benzimidazole proton pump inhibitors. The invention also claims that the bioavailability of the benzimidazole compound is enhanced relative to a pellet or granule-containing formulations.

US 6379705 describe pellet pharmaceutical preparations containing substituted benzimidazoles. The preparations comprise a spherical inert core which is coated with an active layer containing at least one substituted benzimidazole or its salt in the micronized form, which is coated in turn with an insulating layer consisting of a water soluble polymer and coated lastly with a gastroresistant or enteric layer. The pellets produced are placed in hard gelatin capsules for oral administration.

WO9852564 describes pharmaceutical composition, which is a solid pellet comprising an inert core, a benzimidazole in or on the core and a moisture resistant coating comprising at least one hydrophobic material and an enteric coating around the moisture resistant coating.

Despite different approaches disclosed in the art, there exists a need to develop a stable pellet formulation of rabeprazole, which provides comparable or higher bioavailability to marketed formulation of rabeprazole.

Prokinetic agents are those medications that work by increasing the movement of materials through the GI tract. Motility of the GI tract is mediated via smooth muscle cell response to neurotransmitters. The neuronal regulation of gastric motility involves stimulation by cholinergic neurons, inhibition (generally) by adrenergic neurons and complex modulatory influence of enteric nervous system, in which dopamine and serotonin play a role. Thus antagonists of D₂ and 5HT₃ receptors as well as agonists of 5HT₄ receptors can stimulate gastric motility frequently in ways that depend on cholinergic transmission. Prokinetic agents of the first generation, *e.g.* bethanecol, stimulates cholinergic receptors and of the second generation, *e.g.* domperidone and metoclopramide, blocks effects of endogenous dopamine in the gut. The action of the third generation prokinetic agents, such as substituted benzamides, *e.g.* cisapride and mosapride derives primarily, but not exclusively, from facilitating acetylcholine release from neurones of the myenteric plexus via stimulation of 5-HT₄ receptors. The efficacy of orally administered prokinetic agents in patients with GERD and reflux oesophagitis has been studied and a superior effect in alleviating gastro esophageal

symptoms and healing low grade oesophagitis (non circumferential erosion) has been shown in most studies.

Mosapride, chemically known as 4-AMINO-5-CHLORO-2-ETHOXY-N- [4- (4-FLUOROPHENYL) METHYL]-2- MORPHOLINYL] METHYL]-BENZAMIDE, is disclosed in EP243959 and US4870074 as gastrointestinal prokinetic agent. Mosapride is 5-HT₄ agonist intended for oral treatment of gastrointestinal motility disorders. It is known to exert its action by facilitating acetylcholine release from the enteric cholinergic neurons. With respect to the therapeutic actions, mosapride enhances gastric emptying and also improves total acid clearance time. Conditions or symptoms relieved by the promotion of gastric emptying include but are not limited to gastric stasis, flatulence, dyspepsia, peptic ulcer and reflux oesophagitis. Mosapride, a prokinetic agent is also used in the present invention.

Mosapride has a bioavailability of 8% and has elimination half-life of 1.4 to 2.0 hrs (Sakashita M, et al, Arzneimittelforschung. 1993 Aug;43(8):867-72). Hence, conventional release formulation cannot maintain required plasma concentration for long time and is therefore given 3-4 times a day (Drugs of the future, 1993, 513-515). It is a safe drug. Most of the studies have reported no serious side effects of mosapride even at higher dose (Drugs Res., 1993, 867-872; J Pharmacol Expt ther, 1997, 220-227). Mosapride is a selective 5-HT₄ receptor agonist and does not interact with other receptor types. It has a very favorable tolerability profile, with only minor adverse effects such as headache. Unlike other prokinetic agents, mosapride does not cause extrapyramidal symptoms or endocrine disorders. Although, there were rare reports of mosapride associated with QT interval prolongation, the reported incidences occurred when mosapride was used with other pro-arrhythmic drugs.

Considering the above aspects, a sustained release formulation of mosapride would be of great use. The potential advantages of sustained release mosapride over conventional mosapride are as follows;

- Increased patient compliance because of less frequent drug administration.
- The sustained therapeutic plasma levels with this formulation would be maintained for 24 hours.

This would make the drug administration meal independent and would also prevent the regurgitation (GERD) even during sleep.

Patients with mild symptoms of Gastro esophageal reflux disease and limited mucosal damage respond best to H₂-receptor antagonist, prokinetic agents or proton pump inhibitors. But in case of severe symptoms, severe mucosal damage or both are almost always treated with proton pump inhibitors for profound and long-term control of gastric acid secretion. However, due to the wide diversity of symptoms and disease severity produced by acid reflux has led to the need for more individualized treatment strategies

Proton pump inhibitors and prokinetic agents are frequently co-prescribed in the management of GERD. A prokinetic agent prevents reflux while proton pump inhibitors reduce acid secretion. Thus the combination provides complementary actions in abating the symptomatology and in controlling the disease. Moreover, there is no adverse drug interaction reported between both the drugs.

A combination therapy of a prokinetic agent and a gastric acid lowering compound has been found rational and more effective than mono therapy apart from full dose of proton pump inhibitors in different studies. Administration of cisapride and ranitidine was shown to further lower the exposure of the oesophagus to acid(s) (Inauen W et al. Gut 1993; 34: 1025-1031). Such a therapy was also shown to improve healing rates (de Boer WA et al. Aliment Pharmacol Ther 1994; 8: 147-157). WO 95/01803 describes a pharmaceutical composition of famotidine, cisapride and optionally simethicone in the treatment of gastrointestinal distress.

Further, Vyneri et al (N. Engl. J Med 1995; 333: 1106-1110) found that omeprazole alone or in combination with cisapride was more effective than ranitidine alone or cisapride alone and that omeprazole combined with cisapride was more effective than ranitidine plus cisapride. Such combination therapies might be considered for patients whose predominant symptom is regurgitation; those whose symptoms occur mainly at night; those with respiratory problems such as posterior laryngitis, asthma, chronic bronchitis, or recurrent aspiration; those with cough and hoarseness related to reflux disease.

Thus, a combination therapy comprising an acid suppressing agent and a prokinetic agent is attractive, rational and effective. An acid suppressing agent plus a prokinetic agent could be an alternative to each of them separately in case of failure. However, because of the large number of tablets/pills that must be taken each day in such a therapy, the compliance of such a treatment may be a problem. It is well known that patient compliance is a main factor in receiving good results in medical treatments. Administration of two, three or even more different tablets to the patient is not convenient or satisfactory to achieve the most optimal results.

The combination of a proton pump inhibitor and a prokinetic agent, where the proton pump inhibitor is as delayed release and the prokinetic agent is, as sustained release will provide following advantages over the available dosage forms:

- Combination of a proton pump inhibitor and a prokinetic agent has synergistic effect.
- Similar duration of action of proton pump inhibitor and sustained release prokinetic agent.
- Ease of administration and better compliance because of single daily administration.
- Effective in controlling nocturnal esophageal reflux due to prolonged duration of action.

- No overlap in adverse drug reactions. The combination will have the lowest possible daily therapeutic dose of the respective drugs, which makes it less vulnerable to cause any sorts of side effects.
- No Adverse drug interaction.

US6132771 describes a multiple unit tablet dosage form comprising a proton pump inhibitor in the form of enteric coated pellets and one or more prokinetic agents in a fixed formulation.

Currently, there is no commercially available stable formulation of rabeprazole pellets either alone or in combination with a prokinetic agent in a single dosage form, which provides an effective approach for the treatment of GERD and increases patient compliance as well as provides comparable or superior bioavailability with respect to the marketed formulations of rabeprazole. Thus, there is a need to prepare a pharmaceutical composition, which fulfils the aforesaid objectives. The said combination can be either in the form of rabeprazole in a delayed release form either alone or with the prokinetic agent in an immediate release and / or sustained release form.

OBJECTS OF THE INVENTION

An object of the present invention is to provide a stable pharmaceutical composition comprising rabeprazole and one or more prokinetic agent.

Another object of the present invention is to provide a stable pharmaceutical composition comprising rabeprazole in a form of an enteric coated pellet and one or more prokinetic agent in a sustained release form.

Another object of the present invention is to provide a stable pharmaceutical composition comprising rabeprazole in a form of an enteric coated pellet and mosapride in a form of sustained release tablet.

Still another object of the instant invention is to provide a stable pharmaceutical composition comprising rabeprazole in an enteric coated pellet form.

A still further object of the present invention is to provide a process for the preparation of said pharmaceutical composition.

Another object of the invention is to prepare a pharmaceutical composition, which is useful for the treatment and prevention of acid related gastrointestinal disorders particularly gastroesophageal reflux disorders.

Another object of the invention is to prepare a fixed dose oral pharmaceutical composition containing rabeprazole and mosapride, administrable to a mammal in need thereof.

SUMMARY OF THE INVENTION

The present invention relates to stable pharmaceutical composition comprising rabeprazole in a form of pellets either alone or in combination with one or more prokinetic agent in a sustained released form, wherein the said formulation provides enhanced bioavailability of rabeprazole in comparison to tablet formulation of rabeprazole.

Further, the present invention relates to a stable pharmaceutical composition comprising rabeprazole sodium in the form of enteric coated pellets in combination with mosapride citrate dihydrate in the form of sustained release tablet, wherein the bioavailability of rabeprazole is increased by about 1.5 to 2.5 fold with respect to the marketed tablet formulation.

The present invention provides a use of the said formulation for the treatment and prevention of acid related gastrointestinal disorders, preferably gastroesophageal reflux disorders.

The present invention also discloses the process for the preparation of said pharmaceutical preparation.

DETAILED DESCRIPTION OF INVENTION

The present invention relates to stable pharmaceutical composition comprising rabeprazole either alone or in combination with one or more prokinetic agent and pharmaceutically acceptable excipients. In the instant invention, rabeprazole is present in a form of enteric coated pellets and the prokinetic agent in a sustained release form.

In a preferred embodiment, the present invention discloses a pharmaceutical composition of rabeprazole sodium in a form of enteric coated pellets in combination with mosapride citrate dihydrate, in a form of sustained release tablet.

In another embodiment, the present invention discloses a pharmaceutical composition of rabeprazole sodium in a form of enteric coated pellets.

In the present invention, we have surprisingly found that the bioavailability of rabeprazole is enhanced in comparison to the marketed tablet formulation of rabeprazole, when rabeprazole sodium is formulated in a form of enteric coated pellets, either alone or in combination with mosapride citrate dihydrate in a form of sustained release tablet. It has been found that the bioavailability of rabeprazole in enteric coated pellet form is enhanced by around 1.5 to 2.5 fold. Considering this substantial increase in bioavailability, the dose of rabeprazole sodium can be reduced by about 40 to 60%, preferably by about 50 %, when formulated either alone or in combination with a prokinetic agent.

The preparation of enteric coated pellets of rabeprazole and sustained release tablet of one or more prokinetic agent is described in the instant invention.

The formulation disclosed in the present invention is not a mere admixture but has properties different from the sum total of the properties of its ingredients.

The term "rabeprazole" as used herein includes rabeprazole, a pharmaceutically acceptable salt of rabeprazole, a single enantiomer of rabeprazole or a pharmaceutically acceptable salt of the single enantiomer.

The term "prokinetic agent" as used herein includes prokinetic agent or its pharmaceutically acceptable salt.

The term "mosapride" as used herein includes mosapride or its pharmaceutically acceptable salt.

The term "sustained release" as used herein in relation to the composition according to the invention means release, which is not immediate release and is taken to encompass controlled release, sustained release, prolonged release, timed release, retarded release, extended release, delayed release etc.

The term "inert core" as used herein in relation to the composition according to the invention means ethyl cellulose or any inert material coated sugar globules or microcrystalline cellulose spheres or any other inert material spheres.

The pharmaceutical composition of the present invention typically comprises from 5mg to 100mg of rabeprazole. The formulation of this invention preferably comprises 10mg to 40mg rabeprazole.

The amount of prokinetic agent in the pharmaceutical formulation is from 1mg to 50mg. In a preferred embodiment, the amount of prokinetic agent is 2mg to 20mg.

The amount of mosapride in the pharmaceutical formulation is from 1 to 50 mg. In a preferred embodiment, the amount of mosapride is 2 to 20 mg.

The pharmaceutical composition of the present invention may be administered either twice daily or once daily.

The pharmaceutical composition of the instant invention comprises rabeprazole sodium, optionally with one or more prokinetic agent and pharmaceutically acceptable excipients selected from the group comprising of pH modulator, stabilizing agent, diluent, binder or film forming polymer, enteric polymer, disintegrant, anti-sticking agent, plasticizer, rate controlling agent, glidant, coloring agent, aqueous or non-aqueous solvent and other pharmaceutically acceptable excipient or adjuvant.

The prokinetic agent in the instant invention can be selected from the group comprising of first, second and third generation prokinetic agents like cisapride, dazopride, mosapride, exepanol, lincopride, motilin, idremcinal, mitemcinalum, neurotrophin-3, KC-11458, MKC-733, Braintree-851, zacopride, ecabapide, prucalopride, fedotozine, cinitapride, itopride, polycarbophil, tegaserod, INKP-100, diacol, metoclopramide, domperidone, etc.

The pH modulator can be selected from the group comprising of magnesium oxide, dibasic calcium phosphate anhydrous, tribasic calcium phosphate, precipitated calcium carbonate and cellulose derivatives including powdered cellulose and other materials known to one of ordinary skill in the art. The pH modulator in the dosage form ranges from 1 % to 30 % by weight.

Stabilizing agents can be selected from the group comprising of calcium carbonate, dibasic calcium phosphate dihydrate, calcium sulphate anhydrous, calcium sulphate dihydrate, magnesium oxide, magnesium carbonate, magnesium silicate, potassium bicarbonate, potassium hydroxide, dibasic potassium phosphate, sodium hydroxide, sodium bicarbonate, sodium carbonate, dibasic sodium phosphate, tribasic sodium phosphate, magnesium lactate, magnesium gluconate, aluminium hydroxide, sodium citrate, sodium

tartarate, sodium polyphosphate, potassium polyphosphate, sodium acetate, calcium acetate, potassium metaphosphate, calcium glycerophosphate, calcium lactate, calcium bicarbonate and other materials known to one of ordinary skill in the art. Stabilizing agents in the dosage form ranges from 1 % to 30 % by weight.

pH modulator and stabilizing agents and its amount in the present formulation is selected in such a way that the pH of the formulation is maintained at a level so as the minimal degradation of rabeprazole is achieved.

Diluents can be selected from the group comprising of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered and its derivatives, dextrans, dextrans, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch and its derivatives, sucrose, sugar compressible, sugar confectioners and other materials known to one of ordinary skill in the art. Diluents in the dosage form ranges from 10% to 50% by weight.

Binder or film forming polymer can be selected from the group comprising of polyvinyl pyrrolidone, hydroxypropyl methyl cellulose, acacia, alginate derivatives, hydroxy propyl cellulose, carboxymethylcellulose sodium, compressible sugar, ethyl cellulose, gelatin, liquid glucose, methyl cellulose, pregelatinized starch and other materials known to one of ordinary skill in the art. Binders in the dosage form ranges from 1 % to 10 % by weight.

The enteric coating polymers can be selected from the group comprising of Eudragit L12.5 P, Eudragit L 12.5, Eudragit L 100, Eudragit L 100-55, Eudragit L30D55, Eudragit S12.5 P, Eudragit S 12.5, Eudragit S 100, Hydroxypropyl Methylcellulose Phthalate, Polyvinyl acetate phthalate, Cellulose acetate phthalate, shellac and other materials known to one of ordinary skill in the art. Enteric coating polymers in the dosage form ranges from 5 % to 20 % by weight.

Disintegrants can be selected from the group comprising of starch, sodium starch glycolate, croscarmellose sodium, crospovidone, alginate derivatives, carboxy methyl cellulose sodium, guar gum and other materials known to one of ordinary skill in the art. Disintegrants in the dosage form ranges from 0.5 % to 15 % by weight.

Anti-sticking agent can be selected from the group comprising of stearate derivatives like magnesium stearate, calcium stearate, zinc stearate, polyethylene glycol (various grades), talc, hydrogenated castor oil, silica, colloidal silica, cornstarch, calcium silicate, magnesium silicate, silicon hydro gel and other materials known to one of ordinary skill in the art. Anti-sticking agents in the dosage form ranges from 0.1 % to 5 % by weight.

Plasticizers can be selected from the group comprising of dibutyl sebacate, polyethylene glycol and polypropylene glycol, dibutyl phthalate, diethyl phthalate, triethyl citrate, tributyl citrate, acetylated monoglyceride, acetyl tributyl citrate, triacetin, dimethyl phthalate, benzyl benzoate, butyl and/or glycol esters of fatty acids, refined mineral oils, oleic acid, castor oil, corn oil, camphor, glycerol and sorbitol polyethylene glycols, propylene glycol, glycerols, glycerides, fractionated coconut oil and castor oil, ester of a citric acid, phthalic acid or sebacic acid, or a mixture thereof. An ester selected from the group consisting of phthalate esters, phosphate esters, citrate esters, fatty acid esters and tartarate esters, glycerine or glycol derivatives, or sorbitol and other materials known to one of ordinary skill in the art. Plasticizer in the dosage form ranges from 1 % to 20 % by weight.

The rate controlling agents can be selected from the group comprising of cellulosic polymers such as ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxy methyl cellulose, hydroxyl methylcellulose and hydroxyethylcellulose, waxes, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate and methacrylic acid polymers such as Eudragit RL and RS, polymethacrylates, sodium carboxymethylcellulose, calcium carboxymethylcellulose, acrylic acid polymer, polyethylene glycol,

polyethylene oxide, carrageenan, cellulose acetate, zein, carbohydrate gums, polyuronic acid salts, cellulose ethers and acrylic acid polymers. The carbohydrate gums may be one or more of xanthan gum, tragacanth gum, gum karaya, guar gum, acacia, gellan and locust bean gum. The polyuronic acid salts may be one or more of alkali metal salts of alginic acid and pectic acid and other materials known to one of ordinary skill in the art. The rate controlling agent in the dosage form ranges from 10 % to 50 % by weight.

Aqueous or non-aqueous solvents can be selected from the group comprises ethanol, methanol, iso-propanol, water and other known to one of ordinary skill in the art.

Glidants can be selected from the group comprising of colloidal silicon dioxide, cornstarch, talc, calcium silicate, magnesium silicate and other materials known to one of ordinary skill in the art. Glidants in the dosage form ranges from 0.1% to 10 % by weight.

Other pharmaceutical solvents are selected from the group comprising of acetone, dichloromethane, Isopropyl alcohol, Methanol, water etc.

Coloring agent is selected from the group comprising of iron oxides and its derivatives like red oxide of iron, yellow oxide of iron etc. lake and dye colors and colors which are pharmaceutically acceptable.

The preparation of pharmaceutical composition of the present invention comprises of two phases:

Phase-1: Preparation of rabeprazole sodium enteric coated pellets comprising ethyl cellulose or any other inert material coated sugar globules or microcrystalline cellulose spheres or any other inert material spheres of 10 mesh to 100 mesh size, preferably 20 mesh to 30 mesh size. These globules are further coated by addition of an alkali agent to make the drug stable on it. These globules are further coated by a material containing active pharmaceutical ingredient and alkali material as stabilizer. This stabilizer is

used here to maintain the pH of the said layer at not less than 9, preferably 10.5. Further the said globules are coated with barrier coating comprising inert polymers. Then, the same barrier coated globules are coated with an enteric polymer.

Phase-2: Preparation of sustained release portion of prokinetic agent comprising an immediate release portion and sustained release portion of prokinetic agent.

Phase-1: Preparation of rabeprazole sodium enteric coated pellets comprising the following steps:

1. Ethyl cellulose or any inert material coated sugar globules or microcrystalline cellulose spheres or any other inert material spheres of 10 mesh to 100 mesh size preferably 20 mesh to 30 mesh size is taken as an inert core. Inert coating of inert material coated sugar globules is done by spraying the spraying solution on to the ethyl cellulose coated sugar globules on a Wurster spray (Glatt). The spraying solution is prepared by following method:

Binder or film forming polymer(s) is dissolved in water. Anti-sticking and pH modulator are milled together in the presence of a sufficient quantity of water in a colloidal mill. The above milled dispersion is added to the binder or film forming polymer(s) solution and stirred to get a clear homogeneous suspension and the same is passed through Sieve No.100

2. Seal coated sugar globules prepared in step 1 are further coated by the suspension containing active ingredient i.e. rabeprazole sodium in dissolved / disperse form. The coating of active ingredient is done by spraying the coating solution comprising active ingredient on to the inert material coated sugar globules (prepared in step 1) by Wurster spray (Glatt). The coating solution comprising active ingredient is prepared by the following method.

Binder or film forming polymer(s) is dissolved in water. The pH modulator is milled with a sufficient quantity of water in a colloidal mill to get suspension. The pH modulator and rabeprazole sodium are dissolved / disperse in a sufficient quantity of water. The above prepared solution of binder or film forming polymer(s) and suspension of pH modulator is added to the solution of rabeprazole sodium in water and stirred to get a clear suspension and passed through Sieve No.100

3. Further, barrier coating is applied to the globules prepared in step 2 above by Wurster spray (Glatt). The barrier or film forming polymer(s) coating suspension is prepared by following method:

Binder or film forming polymer(s) is dissolved in water. The pH modulator and anti-sticking agent are milled with a sufficient quantity of water in a colloidal mill. This prepared suspension of pH modulator is added to the solution of binder or film forming polymer(s) in water and stirred to get a homogenous suspension and passed through Sieve No. 100.

4. Further, the coated globules prepared in step 3 are coated by an enteric coating polymer(s) and excipients. The coating is applied by Wurster spray (Glatt). The suspension for enteric coating is prepared by the following method.

The plasticizer is dissolved in water. The anti-sticking agent is milled with a sufficient quantity of water in a colloidal mill. The solution of plasticizer and anti-sticking agent dispersion is added to the enteric coating polymer solution or suspension and stirred gently to get a homogeneous suspension and passed through Sieve No.100 to form pellets.

5. The pellets prepared by steps 1 to 4 are filled in capsule, compressed into tablets, added in dry suspension or ready for use suspension, sachets, or formulated as dispersible tablets.

Phase-2: Preparation of prokinetic agent sustained release composition by following steps:

The sustained release composition of prokinetic agent comprises immediate release (IR) portion and sustained release (SR) portion or only sustained release portion.

(A) Immediate release portion of prokinetic agent tablet is prepared by following steps:

1. The prokinetic agent mosapride or its salt is passed through Mesh No.100, red oxide of iron and yellow oxide of iron are passed through Mesh No.150. Diluents are passed through Mesh No. 40.
2. The sifted material is blended together.
3. Binder is dissolved in purified water and is used as the granulating solution to prepare granules of the above blend till the mass of required consistency is obtained.
4. The wet mass obtained in step 3 above is passed through mesh No. 08 and the wet granules dried in a tray dryer at 70°C till the loss on drying is 1.59%.
5. The dried granules are passed through mesh No. 20 and blended with a compression mixture comprising of glidant colloidal silicon dioxide, disintegrating agent and lubricant, previously sieved through mesh No. 60.
6. The granules prepared in step 5 can be used as such or compressed into a tablet or mini tablets or pellets.

(B) Sustained release portion of prokinetic agent tablet is prepared by following steps:

1. The prokinetic agent mosapride is passed through Mesh No. 100. Diluent lactose and rate controlling polymer are passed through Mesh No. 40.
2. The sifted materials of step 1 are blended together.
3. Binder is dissolved in non-aqueous solvent and is used as the granulating solution to prepare granules of the above blend till mass of required consistency is obtained.
4. The wet mass is passed through Mesh No. 08.
5. The wet granules are dried in a tray dryer at 70°C till the loss on drying is 1.81%.
6. The dried granules are passed through Mesh No. 20 and blended with a compression mixture comprising of glidant and lubricant, previously sieved through Mesh No. 60.
7. The granules prepared in step 6 can be compressed into a tablet or mini tablets or pellets.

Rabeprazole pellets obtained by phase I can be formulated in different ways but not limited to pellets filled in capsule, pellets compressed into tablets, pellets in dry suspension or ready for use suspension, sachets and dispersible tablets.

Rabeprazole pellets obtained by phase I, preparation of fraction A of phase – II and preparation of fraction B of phase – II can be combined into a final formulation in different ways but not limited to pellets filled in capsule or pellets compressed into tablets or mini tablets filled in capsule and along with bi-layer tablet prepared from fraction A and B (IR and SR respectively) filled into capsule.

Throughout this specification and the appended claims it is to be understood that the words “comprise” and “include” and variations such as “comprises”,

“comprising”, “includes”, “including” are to be interpreted inclusively, unless the context requires otherwise. That is, the use of these words may imply the inclusion of an element or elements not specifically recited.

The present invention has been described by way of example only and it is to be recognized that modifications thereto which fall within the scope and spirit of the appended claims and which would be obvious to a skilled person based upon the disclosure herein, are also considered to be included within the invention.

PREPARATORY EXAMPLE OF THE DOSAGE FORM

Example – 1

Preparation of Rabeprazole and Mosapride SR capsules

The effective amount of active ingredient according to this invention comprises of:

Rabeprazole Sodium.....20mg

(as enteric coated pellets)

Mosapride Citrate dihydrate eq. to

Mosapride Citrate anhydrous.....15mg

(in sustained release form)

Color: Red oxide of Iron and Yellow Oxide of Iron

Preparation of Rabeprazole sodium enteric coated pellets:

The ingredients used in the preparation of Rabeprazole enteric coated pellets containing Rabeprazole Sodium in the instant invention by Wurster spraying (Glatt process) are given below along with the method of preparation of said pellets.

A) Formula for seal coating of sugar globules.

* loss to be considered during process.

Table 1

Ingredients	Quantity Per batch/grams	Percentage by weight
Sugar globules (seal coated)	1000	96.955
Magnesium oxide light	15	1.45
Hydroxy propyl methyl cellulose 6 cps	15	1.45
Talc	1.5	0.145
Purified water	630	-

Procedure

1.45%w/w hydroxypropylmethylcellulose 6 cps was dissolved in water. Milled together 0.145%w/w talc and 1.45%w/w magnesium oxide with sufficient quantity of water in a colloidal mill. Added the milled dispersion of above to the HPMC solution and stirred to get a clear solution and passed through Sieve No.100.

The above solution was sprayed on to the ethyl cellulose coated sugar globules on a Wurster spray (Glatt)

B) Formula for drug coating on seal coated sugar globules:**Table 2**

Ingredients	Quantity Per batch/grams	Percentage by weight
Sugar globules (seal coated) Step A	800	60.859
Rabeprazole sodium	350	26.626
Magnesium oxide light	70	5.325
Hydroxy propyl methyl cellulose 6CPS	87.5	6.656
Sodium hydroxide	7.0	0.534
Purified water	3500	-

Procedure

6.656 % w/w hydroxypropylmethylcellulose 6 cps was dissolved in water. Milled 5.325% w/w magnesium oxide with sufficient quantity of water in a colloidal mill. 0.534% w/w Sodium hydroxide and 26.626 % w/w Rabeprazole sodium were dissolved in sufficient quantity of water. Added the above solution of HPMC and magnesium oxide to the solution of rabeprazole in water and stirred to get homogeneous suspension and passed through Sieve No. 100.

The above suspension was sprayed on to the seal coated sugar globules by Wurster spray (Glatt).

C) Formula for Barrier coating:**Table 3**

Ingredients	Quantity Per batch/grams	Percentage by Weight
Drug coated pellets	1200	86.957
Hydroxy propyl methyl cellulose 6CPS	150	10.869
Magnesium oxide light	15	1.087
Magnesium stearate	15	1.087
Purified water	3600	-

Procedure

10.869 % w/w Hydroxypropyl methylcellulose 6 cps was dissolved in water. Milled 1.0869% w/w magnesium oxide and 1.087 % w/w magnesium stearate with sufficient quantity of water in a colloidal mill. Added the suspension of magnesium oxide and Magnesium stearate into the solution of HPMC in water and stirred to get a homogenous suspension and passed through sieve 100#.

The above suspension was sprayed on to the seal coated sugar globules by Wurster spray (Glatt).

D) Formula for enteric coating:**Table 4**

Ingredients	Quantity Per batch/grams	Percentage by weight
Barrier coated pellets	1300	66.663
Eudragit L 30 D 55	1667.0	25.645
Talc	100	5.128
Polyethylene glycol 6000	50	2.564
Purified water	1400	-

Procedure

2.564 % w/w Polyethylene glycol 6000 was dissolved in water. Milled 5.128 % w/w Talc with sufficient quantity of water in a colloidal mill. Added the solution of Polyethylene glycol 6000 and talc dispersion to 25.645 % w/w Eudragit L30 D 55, stirred gently and passed through Sieve No. 100.

The above suspension was sprayed on to the seal coated sugar globules by Wurster spray (Glatt).

The final pellets were filled in hard gelatin capsules.

Assay	: 102.5 %
Related Impurities	: Single max 0.62
	Total imp 1.62
Karl Fischer Coefficient	: 5.26

Dissolution Profile of Rabeprazole sodium of the instant invention at pH 1.2 simulated gastric fluid

The dissolution of pellets prepared according to the instant invention was determined in a paddle apparatus. The rotation speed was set at 50 ± 2 revolutions per minute, the dissolution medium being 0.1 N HCl maintained at a fixed temperature of 37°C (pH 1.2 simulated gastric fluid). The total volume of the dissolution fluid was 250 ml. The data obtained is presented in Table 5.

Table 5

Product containing 20 mg of Rabeprazole sodium		% DRUG RELEASE
S. NO.	DOSAGE FORM	2 hr
1	Rabeprazole sodium enteric coated Pellets 15.02 % w/w	6.7 (Limit NMT 10 % in 2 hours)

Dissolution Profile of Rabeprazole sodium of the instant invention at pH 10

The dissolution of pellets prepared according to the instant invention was determined in a basket apparatus. The rotation speed was set at 100 ± 2 revolutions per minute, the dissolution medium being pH 10 buffer maintained at a fixed temperature of 37°C. The total volume of the dissolution fluid was 900 ml. The data obtained is presented in Table 6.

Table 6

Product containing 20 mg of Rabeprazole sodium		% DRUG RELEASE
S NO...	DOSAGE FORM	45 min
1	Rabeprazole sodium enteric coated Pellets..... 15.02 % w/w	96.1

The dissolution rate of the pellets prepared in the instant invention was found to be less than 10 % in 2 hours in simulated gastric fluid (pH 1.2) and more than 70 % in 45 minutes at pH 10. Thus, the dissolution of the delayed release pellets of rabeprazole prepared according to the instant invention is acceptable.

Preparation of Mosapride citrate Sustained release tablets

The ingredients used in the preparation of Mosapride citrate sustained release tablets containing Mosapride citrate in the instant invention is given below along with method of preparation of said tablets by wet granulation.

A) Formula for preparation of IR fraction:**Table 7**

Ingredients	Quantity In mg /tab	Percentage by weight
Mosapride citrate dihydrate eq. to Mosapride citrate anhydrous.....4.5mg	4.764	3.285
Lactose	85.0	58.621
Microcrystalline cellulose	43.336	29.886
Red oxide of iron	0.03	0.021
Yellow oxide of iron	0.12	0.083
Polyvinyl pyrrolidone K 30	4.5	3.103
Croscarmellose sodium	5.0	3.45
Colloidal silicon dioxide	0.75	0.517
Magnesium stearate	1.50	1.034
Total	145 mg	100 % w/w

*Potency of the Mosapride citrate adjusted to 100 % & quantity of lactose IP should be reduced to keep input constant.

Procedure

Mosapride citrate 3.285% w/w was passed through Mesh No. 100. 0.021% w/w red oxide of iron and 0.083% w/w yellow oxide of iron, were passed through Mesh No. 150. Lactose 58.621% w/w and microcrystalline cellulose 29.886% w/w were passed through Mesh No. 40. The sifted materials were blended together. 3.103% w/w of polyvinylpyrrolidone K30 was dissolved in 400 ml of purified water and was used as the granulating solution to prepare granules of the above blend till the mass of required consistency was obtained. It required 500 ml of extra purified water. The wet mass was passed through Mesh No. 08 and the wet granules dried in a tray dryer at 70°C till the loss on drying was 1.59 %. The dried granules were passed through Mesh No.20 and blended with a compression mixture comprising of 0.517% w/w of colloidal silicon dioxide, 3.45% w/w of croscarmellose sodium and 1.034% w/w of magnesium stearate, previously sieved through Mesh No. 60.

B) Formula for preparation of Sustained Release fraction:**Table 8**

Ingredients	Quantity In mg /tab	Percentage by weight
Mosapride citrate dihydrate equivalent. to Mosapride citrate anhydrous.....10.5mg	11.117	13.897
Lactose	38.383	47.978
Hydroxypropyl methylcellulose K4M	25.0	31.250
Polyvinyl pyrrolidone K 30	4.0	5.000
Colloidal silicon dioxide	0.5	0.625
Magnesium stearate	1.0	1.250
Total	80 mg	100 % w/w

* Potency of the Mosapride citrate adjusted to 100 % & quantity of lactose IP should be reduced to keep input constant.

Procedure

Mosapride citrate 13.897% w/w was passed through Mesh No. 100. Lactose 47.978% w/w and hydroxypropylmethylcellulose K4M were passed through Mesh No. 40. The sifted materials were blended together. 5.0% w/w of polyvinylpyrrolidone K30 was dissolved in 1000 ml of isopropyl alcohol and was used as the granulating solution to prepare granules of the above blend till the mass of required consistency was obtained. The wet mass was passed through Mesh No. 08 and the wet granules dried in a tray dryer at 70°C till the loss on drying was 1.81%. The dried granules were passed through Mesh No. 20 and blended with a compression mixture comprising of 0.625% w/w of colloidal silicon dioxide and 1.25% w/w of magnesium stearate, previously sieved through Mesh No.60.

The final blend thus obtained comprising of two layers of fraction A and B (IR and SR respectively) were compressed into 225 mg bilayered tablets on a tablet compression machine using 10*5 mm capsule shaped punches.

Assay : 99.03
 Karl Fischer Coefficient : 5.68
 Organic Volatile Impurities (IPA) : 1557ppm

Dissolution Profile of Mosapride citrate of the instant invention at pH 1.2 (simulated gastric fluid)

The dissolution of tablets prepared according to the instant invention was determined in a Paddle apparatus. The rotation speed was set at 50 ± 2 revolutions per minute, the dissolution medium being 0.1 N HCl maintained at a fixed temperature of 37 °C (pH 1.2 simulated gastric fluid). The total volume of the dissolution fluid was 900 ml. The data obtained is presented in Table 9.

Table 9

PRODUCT CONTAINING 15 MG UNCOATED TABLET		% DRUG RELEASE AT DIFFERENT TIME INTERVAL						
		Hours						
SL NO	DOSAGE FORM	1	2	4	6	8	10	12
1.	Mosapride citrate sustained release tablets	38.4	48.5	64.1	76.3	87.3	92.1	100.5

Thus, the dissolution rate of the mosapride citrate sustained release tablets prepared in the instant invention was found to be acceptable.

The final pellets of the rabeprazole and mosapride tablet are than filled in hard gelatin capsules.

Example II

Six month stability profile of Rabeprazole and mosapride citrate SR capsules

Table 10

<i>Condition/ Period</i>	<i>Assay (%)</i>		<i>RI</i>		<i>% Dissolution Rabeprazole</i>		<i>% Dissolution Mosapride.(hr)</i>		
					<i>GF</i>	<i>IF</i>			
	Rabe.	Mosa.	single	total	2 hrs	45min	1	6	12
Initial	102.5	99.03	0.62	1.62	6.7	96.1	38.4	76.3	100.5
40°C 75%RH 1 M	97.2	102	--	--	5.0	95.4	38.7	73.8	
40°C 75%RH 3 M	97.7	100.2	--	--	5.8	97.9	40.1	79.8	101.6
40°C 75%RH 6 M	94.32	99.21	0.47	2.07	8.4	95.7	39.5	77.8	104.2
30°C 65%RH 3 M	99.1	99.5	--	--	2.7	101.5	40.4	80.1	103.3
30°C 65%RH 6 M	95.91	100.13	0.26	1.24	4.9	97.4	39.4	78.1	103.8

Example III

Six month stability profile of Rabeprazole pellets filled in Capsules and rabeprazole tablets.

Table 11

<i>Condition/ Period</i>	<i>Rabeprazole Pellets</i>			<i>Rabeprazole Tablets (Veloz)[§]</i>		
	<i>Assay (%)</i>	<i>RI</i>		<i>Assay (%)</i>	<i>RI</i>	
	<i>Rabeprazole</i>	<i>Single</i>	<i>total</i>	<i>Rabeprazole</i>	<i>single</i>	<i>total</i>
Initial	100.03	0.62	1.62	97.07	-	-
40°C 75%RH 1 M	100.3	0.49	1.08	96.1	0.4	1.1
40°C 75%RH 3 M	96.7	0.59	1.23	96.7	0.69	1.76
40°C 75%RH 6 M	94.35	0.21	1.17	94.3	1.14	4.66
30°C 65%RH 3 M	97.9	0.67	1.76	--	--	--
30°C 65%RH 6 M	94.90	0.33	1.35	--	--	--

[§] Veloz – Rabeprazole enteric coated tablet – Manufactured by Torrent Pharmaceuticals Ltd.

Above data confirms that pellets are more stable than tablet formulations

Example-IV**Bioequivalence study**

We have conducted two Pharmacokinetic studies on Rabeprazole 20 mg in healthy human Volunteers.

The first study (Study I) was a bioavailability study conducted comparing Rabeprazole as enteric coated pellets in the Fixed Dose Combination (FDC) of Rabeprazole 20mg + Mosapride SR 15 mg capsule formulation, with co-administration of VELOZ (Rabeprazole Tablet formulation; Torrent

Pharmaceuticals Limited, India) and MOSID OD (Mosapride SR 15 mg Tablet formulation; Torrent Pharmaceuticals Limited, India).

The second study (Study II) was a bioequivalence study conducted at Torrent Research Centre with 12 volunteers comparing test formulation (Rabeprazole 20mg Tablet of Torrent Pharmaceuticals Ltd) with Reference formulation "PARIET" (Rabeprazole sodium 20mg tablet of EISAI Pharma UK).

We compared Pharmacokinetic Parameters of Rabeprazole 20 mg from both these studies.

Since the sampling time points were different in two studies we took only those time points that were common to both the studies for the calculation of Pharmacokinetic Parameters. For the statistical calculation plasma concentrations derived at Pre-dose and 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0 and 10.0 hours were considered. Original time points for Study 1 was Pre-dose and 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0 and 10.0 hours after study drug administration and for Study 2 Pre-dose and 0.5, 0.75, 1.0, 1.25, 1.50, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0 and 12.0, hours after study drug administration. This was done to take care of sampling time points variations in the two studies that were likely to affect the mean concentrations for C_{max} , $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$.

The derived C_{max} and AUC for Rabeprazole in the two studies are given in the table 12 below.

Table 12

Study	Group	Formulation	C_{max} (ng/ml)	$AUC_{(0-t)}$ (ng/ml*hr)	$AUC_{(0-\infty)}$ (ng/ml*hr)
I	A	Rabeprazole Pellet* + Mosapride citrate dihydrate (15 mg) in capsule	937.685 ± 219.35	1698.486 ± 565.52	1749.330 ± 589.05
	B	Rabeprazole* (Veloz tablet) + Mosapride citrate dihydrate (15 mg) (MOSID OD tablet)	355.749 ± 331.05	877.901 ± 609.77	975.748 ± 608.43
II	C	Rabeprazole* (Veloz tablet)	511.076 ± 231.13	928.193 ± 598.20	1035.218 ± 641.62
	D	Rabeprazole* (Pariet tablet)	354.238 ± 191.84	624.239 ± 362.58	902.564 ± 334.57

* Enteric coated

AUC_(0-∞) – Area under the curve from zero to infinity.

C_{max} – The peak plasma concentration achieved after the administration of the drug.

With the tablet formulation of Rabeprazole (Group B, C, & D) the observed C_{max} was within the range of 354.238 ± 191.84 to 511.076 ± 231.13 whereas with the Rabeprazole capsules containing pellets (Group A) the C_{max} was 937.685 ± 219.35 . Similarly, for AUC_(0-∞) with the tablet formulation of Rabeprazole (Group B, C, & D) the observed AUC was within the range of 902.564 ± 334.57 to 1035.218 ± 641.62 whereas for the Rabeprazole capsules containing pellets (Group A) the AUC was 1749.330 ± 589.05 .

For AUC, there was no significant difference between Groups B, C & D. The observed AUC for Group A was significantly higher ($p < 0.001$) as compared to Group B, C & D.

The C_{max} was also significantly higher ($p < 0.001$) for Group A as compared to Group B, C & D.

Mosapride was administered either as FDC or co-administered with Rabeprazole in the first study.

Thus, it can be concluded that the bioavailability of rabeprazole in pellet form is significantly higher as compared to that of Rabeprazole tablet (Veloz and Pariet)

CLAIMS

1. A stabilized pharmaceutical composition comprising rabeprazole, optionally with one or more prokinetic agent and one or more pharmaceutically acceptable excipients, wherein the said composition provides enhanced bioavailability of rabeprazole relative to a tablet formulation of rabeprazole.
2. A pharmaceutical composition as claimed in claim 1, wherein the one or more pharmaceutically acceptable excipients comprise pH modulators, stabilizing agents, binders or film forming polymers, enteric polymers, diluents, disintegrants, anti-sticking agents, plasticizers, rate controlling agents, glidants, coloring agents, solvents.
3. A pharmaceutical composition as claimed in claim 1, wherein rabeprazole is in the form of rabeprazole sodium.
4. A pharmaceutical composition as claimed in claim 1, wherein rabeprazole sodium is in the form of enteric coated pellets.
5. A pharmaceutical composition as claimed in claim 1, wherein prokinetic agent is in a sustained release form.
6. A pharmaceutical composition as claimed in claim 1, wherein the bioavailability of rabeprazole is increased up to 1.5 to 2.5 fold.
7. A pharmaceutical composition as claimed in claim 1, wherein prokinetic agent is selected from the group comprising of cisapride, dazopride, mosapride, exepanol, lintopride, motilin, idremcinal, mitemcinalum, neurotrophin-3, KC-11458, MKC-733, Braintree-851, zacopride, ecabapide, prucalopride, fedotozine, cinitapride, itopride, polycarbophil, tegaserod, INKP-100, diacol, metoclopramide, domperidone or pharmaceutically acceptable salt thereof.
8. A pharmaceutical composition as claimed in claim 7, wherein preferred salt of mosapride is mosapride citrate dihydrate.
9. A pharmaceutical composition as claimed in claim 1, wherein the amount of the rabeprazole is in the range of 5mg. to 100mg, preferably in the range of 10mg. to 40mg. and the amount of the prokinetic agent is in the range of 1mg to 50mg, preferably in the range of 2mg. to 20mg..

10. A pharmaceutical composition as claimed in claim 1, wherein the amount of the rabeprazole is in the range of 5mg. to 100mg, preferably in the range of 10mg. to 40mg. and the amount of the mosapride is in the range of 1mg. to 50mg, preferably in the range of 2mg. to 20 mg..
11. A pharmaceutical composition as claimed in claim 2, wherein pH modulator is selected from the group comprising of magnesium oxide, dibasic calcium phosphate anhydrous, tribasic calcium phosphate, precipitated calcium carbonate and cellulose derivatives including powdered cellulose.
12. A pharmaceutical composition as claimed in claim 2, wherein stabilizing agent is selected from the group comprising of calcium carbonate, dibasic calcium phosphate dihydrate, calcium sulphate anhydrous, calcium sulphate dihydrate, magnesium oxide, magnesium carbonate, magnesium silicate, potassium bicarbonate, potassium hydroxide, dibasic potassium phosphate, sodium hydroxide, sodium bicarbonate, sodium carbonate, dibasic sodium phosphate, tribasic sodium phosphate, magnesium lactate, magnesium gluconate, aluminium hydroxide, sodium citrate, sodium tartarate, sodium polyphosphate, potassium polyphosphate, sodium acetate, calcium acetate, potassium metaphosphate, calcium glycerophosphate, calcium lactate and calcium bicarbonate.
13. A pharmaceutical composition as claimed in claim 2, wherein enteric polymer is selected from the group comprising of Eudragit L12.5 P, Eudragit L 12.5, Eudragit L 100, Eudragit L 100-55, Eudragit L30D55, Eudragit S12.5 P, Eudragit S 12.5, Eudragit S 100, Hydroxypropyl Methylcellulose Phthalate, Polyvinyl acetate phthalate, Cellulose acetate phthalate and shellac.
14. A pharmaceutical composition as claimed in claim 2, wherein diluent is selected from the group comprising of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powders and its derivatives, dextrans, dextrins, dextrose, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch and its derivatives, sucrose, sugar compressible and sugar confectioners.

15. A pharmaceutical composition as claimed in claim 2, wherein binder or film forming polymer is selected from the group comprising of polyvinyl pyrrolidone, hydroxypropyl methyl cellulose, acacia, alginic acid, hydroxy propyl cellulose, carboxymethylcellulose sodium, compressible sugar, ethyl cellulose, gelatin, liquid glucose, methyl cellulose and pregelatinized starch.
16. A pharmaceutical composition as claimed in claim 2, wherein disintegrant is selected from the group comprising of starch, sodium starch glycolate, croscarmellose sodium, crospovidone, alginic acid, carboxy methylcellulose sodium and guar gum.
17. A pharmaceutical composition as claimed in claim 2, wherein anti-sticking agent is selected from the group comprising of magnesium stearate, calcium stearate, zinc stearate, polyethylene glycol, talc, hydrogenated castor oil, silica, colloidal silica, corn starch, calcium silicate, magnesium silicate and silicon hydro gel.
18. A pharmaceutical composition as claimed in claim 2, wherein plasticizer is selected from the group comprising of dibutyl sebacate, polyethylene glycol and polypropylene glycol, dibutyl phthalate, diethyl phthalate, triethyl citrate, tributyl citrate, acetylated monoglyceride, acetyl tributyl citrate, triacetin, dimethyl phthalate, benzyl benzoate, butyl and/or glycol esters of fatty acids, refined mineral oils, oleic acid, castor oil, corn oil, camphor, glycerol and sorbitol polyethylene glycols, propylene glycol, glycerols, glycerides, fractionated coconut oil, castor oil, phthalic acid, sebacic acid, or a mixture thereof.
19. A pharmaceutical composition as claimed in claim 2, wherein rate controlling agent is selected from the group comprising of cellulosic polymers such as ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxy methyl cellulose, hydroxyl methylcellulose and hydroxyethylcellulose, waxes, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate and methacrylic acid polymers such as Eudragit RL and RS, polymethacrylates, sodium carboxymethylcellulose, calcium carboxymethylcellulose, acrylic acid

polymer, polyethylene glycol, polyethylene oxide, carrageenan, cellulose acetate, zein, carbohydrate gums, polyuronic acid salts, cellulose ethers and acrylic acid polymers, xanthan gum, tragacanth gum, gum karaya, guar gum, acacia, gellan, locust bean gum, alginic acid and pectic acid

20. A pharmaceutical composition as claimed in claim 2, wherein Aqueous or non aqueous solvent is selected from the group comprising of ethanol, methanol, iso-propanol and water.
21. A pharmaceutical composition as claimed in claim 2, wherein glidant is selected from the group comprising of colloidal silicon dioxide, corn starch, talc, calcium silicate and magnesium silicate.
22. A pharmaceutical composition as claimed in claim 2, wherein pharmaceutical solvents are selected from the group comprising of methanol, acetone and purified water.
23. A pharmaceutical composition as claimed in claim 2, wherein coloring agent is selected from the group comprising of iron oxides and its derivatives like red oxide of iron, yellow oxide of iron, lake and dye colors and the colors which are pharmaceutically acceptable.
24. Process for the preparation of stable pharmaceutical composition comprises rabeprazole sodium enteric coated pellets, wherein an inert core is coated with rabeprazole sodium and enteric coating, characterized in that the inert core, drug coating and enteric coating is separated by an alkaline layers and the bioavailability of rabeprazole is enhanced relative to a tablet formulation of rabeprazole.
25. A process as claimed in claim 24, wherein enteric coated pellets of rabeprazole are filled in a capsule or sachet or compressed into tablets or formulated into a dry suspension or ready for use suspension or dispersible tablets.
26. A process as claimed in claim 25 may further comprise one or more prokinetic agent in a sustained release form.
27. A process as claimed in claim 26, wherein preparation of sustained release formulation of prokinetic agent comprising the steps of preparing immediate release portion and sustained release portion and

subsequently compressing into the bilayered tablet or filled in the capsule.

28. A process as claimed in claim 26, wherein prokinetic agent is mosapride citrate dihydrate.
29. A Process for the preparation of pharmaceutical composition as claimed in claim 26, wherein enteric coated pellets of rabeprazole prepared are encapsulated either alone or with the sustained release prokinetic agent.
30. A pharmaceutical composition as claimed in claim 1 is useful for prevention and treatment of acid related gastrointestinal disorders, preferably gastroesophageal reflux disorders.
31. A pharmaceutical composition substantially as herein described with reference to the foregoing examples.
32. A process for the preparation of the pharmaceutical composition substantially as described with reference to the foregoing examples.
33. A method of achieving a plasma concentration wherein upon administration to a patient of a total dose of about 20mg of pharmaceutical composition as claimed in claim 1 produces AUC_{∞} value of at least 1382 ng/ml*hr of rabeprazole.